REMARKS

Applicants request respectfully that the allowability of the claims be reconsidered in view of the above amendments and the following remarks.

Status of the Claims

Claims 1, 18, 19, 24 to 27, 31, and 32 have been amended. No claims have been added or cancelled. The claims pending presently are Claims 1, 7, 11, 14, 15, 18, and 19 to 32.

Applicants note that Claims 24 to 27, 31 and 32 were subject only to a Section 112, second paragraph, rejection. It is submitted that, as the above amendment overcomes this rejection, it is expected that these claims will be considered to be allowable.

Discussion of the Amendments

Claim 1 has been amended to clarify that the reagent is reacted with the cationic lipids/polymers already present in the DNA-containing complex and the colloid resulting from the process contains complexes which have a neutral or net anionic surface potential. Support for this amendment is found in the application at the third paragraph following the title "Summary of the Invention" on page 3, the paragraph bridging pages 3 and 4, the first paragraph following the title "Detailed Description of the Invention" on page 6, the paragraph bridging pages 6 and 7, and Examples 1 and 2.

Claim 18 has been amended to define the colloid as being one made using the process of Claim 1. Support for this amendment is found in Claim 1.

Claim 19 has been amended to clarify that the colloid referred to therein is the stable colloid defined by Claim 18.

The amendments to dependent Claims 24 to 27, 31, and 32 involve the deletion of the term "process" in favor of the term --method--, the latter term being referred to in Claim 19 on which the claims depend.

No new matter has been added.

Traversal of the Examiner's Section 102 Rejection
of Claims 1, 7, 11, 14, and 15 Based on Monahan et al.

The Examiner rejected independent Claim 1 and Claims 7, 11, 14, and 15, which are dependent thereon, as being anticipated under Section 102(e) by U.S. Patent No. 6,379,966 to Monahan et al. Applicants traverse this rejection.

In order for a disclosure to anticipate a claim, it must disclose each element of the claim. Applicants submit that Monahan et al. does not disclose each element of the claim.

Applicants' claims distinguish over the disclosure of Monahan et al. in that they define a process that involves the step of reacting citraconic anhydride (CCA) or N-hydroxysuccinimide (NHS) acetate with cationic lipids/polymers which are part of a complex containing DNA and cationic lipds/polymers (hereafter "DNA-containing complex"). Monahan et al. does not disclose such a step. Instead, Monahan et al. discloses the reaction of CCA and NHS ester with polymers **which are not part of a DNA-containing complex** to create anionic polymers (see column 25 of Monahan et al.). These anionic polymers are then, in turn, admixed with a complex comprising DNA and cationic lipids/polymers to form an anionic layer surrounding that complex (see column 23, lines 56 to 58, of Monahan et al.). As such, Monahan et al. **does not**

disclose the reaction of CCA or NHS acetate with cationic lipids/polymers already present in a DNA-containing complex.

Applicants' invention is even further distinguished from the disclosure of Monahan et al. respecting the use of NHS esters. In contrast to what the Examiner claims, Monahan et al. does **not** disclose the reaction of NHS esters with cationic polymers to form anionic polymers and applicants have not stated that it does. Rather, Monahan et al. discloses the reaction of NHS ester with **anionic polymers** to link such polymers with disulfide bond-containing moieties to form cleavable anionic polymers with the cleavage site being where the disulfide bond is (see columns 13 and 14 and column 15, lines 26 to 38, of Monahan et al.). These cleavable anionic polymers are then, in turn, admixed with the DNA-containing complex, in the process described above, to form an anionic layer surrounding that complex.

Given the above, it should be abundantly clear that applicants' claims distinguish over the disclosure of Monahan et al. in that applicants' claims recite specifically that CCA or NHS acetate is **reacted with the cationic lipids/polymers already present in a DNA-containing complex** whereas Monahan et al. does not disclose such a step. Monahan et al., therefore, does not anticipate applicants' claims. Accordingly, applicants request respectfully the withdrawal of the Examiner's rejection.

Applicants would like to also submit respectfully that the above argument was made in their previous Reply of July 11, 2005. While the Examiner claimed, in her Action, that the argument was not convincing, her conclusion was based on a misinterpretation of applicants' argument. Specifically, the Examiner misinterpreted applicants as arguing that Monahan et al. does not disclose the reaction of CCA with cationic polymers. Applicants never argued that point and agree that Monahan et al. does disclose the reaction of CCA with cationic polymers. Applicants' argument is,

and has been, that Monahan et al. **does not disclose the reaction of CCA or NHS acetate with the cationic lipids/polymers already present in a DNA-containing complex**.

Traversal of the Examiner's
Section 102 Rejection of Claims 18 to 23 and 30 Based on Monahan et al.

The Examiner has rejected Claims 18 to 23 and 30 as being anticipated under Section 102(e) by the aforementioned Monahan et al. patent.

Independent Claim 18, from which Claims 20 to 23 and 30 depend, defines a stable colloid made using the process of Claim 1 and independent Claim 19 defines the use of such a colloid. As explained above, applicants' process Claim 1 distinguishes clearly over the colloid made by the Monahan et al. process. Applicants' colloid is made by modifying a precursor colloid comprising a complex of DNA and cationic lipids/polymers by reacting the CCA or NHS acetate with the cationic lipids/polymers of the complex to result in a complex which has a neutral or net anionic surface potential. Thus, the complex of applicants' colloid itself has a neutral or net anionic charge. In contrast, the colloid of Monahan et al. comprises a complex of DNA and cationic polymers **which is enveloped by an additional layer of anionic polymers** (see column 23, lines 56 to 59, of Monahan et al.). Applicants' colloid does not require this additional layer.

Given the above, it is abundantly clear that applicants' colloids distinguish over those described in Monahan et al. and, therefore, Monahan et al. does not anticipate applicants' claims. Accordingly, applicants request respectfully the withdrawal of the Examiner's rejection.

Traversal of the Examiner's Section 103 Rejections Based on Monahan et al.

The Examiner has rejected Claims 1, 7, 11, 14, 15, 18 to 23, and 30 (each discussed above) under Section 103 as being obvious in view of Monahan et al. Applicants traverse this rejection.

In order to establish a *prima* facie case of obviousness, the Examiner must show that the cited art teaches or suggests each of the elements of the claimed invention. MPEP §2143.

Claims 1, 7, 11, 14, and 15 define a process which involves the step of modifying a precursor colloid comprising a complex of DNA and cationic polymers/lipids by reacting **the complex** with CCA or NHS acetate. It is clear from the above discussion that this step is not taught or suggested by Monahan et al. Accordingly, the Examiner has not established a *prima facie* case of obviousness with respect to Claims 1, 7, 11, 14, and 15.

Claims 18 to 23 and 30 define a colloid made using the process of Claim 1. As stated above this colloid is entirely different from the colloid formed by the method of Monahan et al. The colloid of Monahan et al. comprises a DNA-cationic polymer complex which is **surrounded by an additional layer of anionic polymers**. While it is true that Monahan et al. discloses the use of CCA to convert cationic polymers into anionic polymers, the resulting anionic polymers are then used to form **the additional layer of anionic polymers** that surrounds the DNA-cationic polymer complex. By contrast, the applicants' colloid includes a DNA-cationic polymer/lipid complex that itself has a neutral or net anionic charge. This is a characteristic that is not disclosed or suggested by Monahan et al. Accordingly, the Examiner has not established a *prima facie* case of obviousness with respect to Claims 18 to 23 and 30.

Given the above, Monahan et al. does not render applicants' claims obvious and the Examiner's Section 103 rejection of Claims 1, 7, 11, 14, 15, 18 to 23, and 30 based thereon should be withdrawn.

Traversal of the Examiner's
Section 103 Rejection Based on Semple et al., Monahan et al., and Trubetskoy et al.

The Examiner has rejected independent Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 30 as being rendered obvious under Section 103(a) by:

(A) U.S. Patent No. 6,287,591 to Semple et al., which discloses the use of a buffer to change the surface potential of a DNA-cationic lipid complex to render it neutral; in view of

(B) Monahan et al., which discloses the use of CCA to react with a cationic polymer to render it anionic and the use of the resulting anionic polymer in the formation of an anionic layer around a DNA-cationic polymer complex; and

(C) U.S. Application Publication No. 2003/0026841 to Trubetskoy et al., which claims priority to a provisional application filed on December 31, 1999 and discloses the use of anionic compounds in the formation of an anionic layer around a DNA-cationic polymer complex and states further that the addition of certain anionic compounds may destabilize the complex.

Neither Monahan et al. nor Trubetskoy et al. teaches the reaction of a reagent with the cationic lipids/polymers already present in a DNA-cationic lipid/polymer complex.

The Examiner argues that one skilled in the art would have been motivated by Trubetskoy et al. to modify the DNA-cationic lipid complexes of Semple et al. by adding anionic compounds and been further motivated by Monahan et al. to create such anionic compounds by reacting cationic polymers with CCA or NHS ester (as stated above, the Examiner is incorrect in her belief that Monahan et al. discloses the use of NHS ester to react with cationic polymers). Applicants traverse the Examiner's rejection.

In order to establish a *prima facie* case of obviousness, the Examiner must show that there is reason for one skilled in the art to believe that applicants' claimed invention would be successful for its intended purpose. MPEP §2143. The Examiner has failed to show that one skilled in the art would have had any expectancy of success. Indeed, as explained below, one of the cited references refers to the unpredictability that results when an anionic compound is added to a DNA-cationic lipid/polymer complex.

The rejected claims are directed to: (A) a process for making a **stable colloid** for gene transfer comprising the step of modifying a precursor colloid which includes a complex which comprises DNA and cationic lipids/polymers and has a cationic surface potential by reacting CCA or NHS acetate with the cationic lipids/polymers present in the complex so that the surface potential of the resulting complex is rendered neutral or net anionic; (B) a stable colloid made using such a process; and (C) a method for using such a colloid.

Prior to applicants' invention, one skilled in the art would not have had any expectancy that the modification of a precursor colloid by reacting CCA or NHS acetate with the cationic lipids/polymers of a DNA-cationic lipid/polymer complex therein would result in a stable colloid. Such a reaction effectively coverts some of the cationic lipids/polymers in the complex into neutral or anionic lipids/polymers. As

stated in Trubetskoy et al. (see paragraph [0043] thereof), the result of the addition of anionic compounds to a DNA-cationic lipid/polymer complex is unpredictable as the addition of certain anionic compounds may lead to destabilization of the complex. This is because the DNA-cationic lipid/polymer complex is held together by the electrostatic interaction of DNA, which is negatively charged, with the cationic lipids/polymers. The addition of certain anionic compounds may disrupt this. For example, depending upon the type of anionic compound used, the cationic lipids/polymers may interact solely with the anionic compound and no longer complex with the DNA. Thus the stability of applicants' colloid can not be predicted simply because colloids comprising DNA-cationic lipid/polymer complexes to which other anionic compounds have been added are stable. Accordingly, without a prior teaching or suggestion that the reaction of CCA or NHS acetate with the cationic lipids/polymers in a DNA-containing complex would result in a stable colloid, one skilled in the art would not have had any expectancy that applicants' invention would produce stable colloids.

While Monahan et al. does teach the use of CCA (but not NHS acetate) to modify a cationic polymer and render it anionic, it does not teach or suggest such modification with respect to a cationic polymer which is already present in a DNA-containing complex. Rather it teaches the creation of such an anionic polymer separate and apart from the DNA-containing complex and the subsequent addition of the resulting anionic polymers to form an anion. This is entirely different from what occurs in applicants' process wherein CCA or NHS acetate is reacted with cationic lipids/polymers that are part of the DNA-containing complex to render them neutral or anionic. Applicants' process not only results in the effective addition of neutral or anionic lipids/polymers to the complex (by way of conversion of cationic polymers/lipids therein) but also in a net loss of cationic lipids/polymers from the complex. One of skill in the art would, therefore, expect that there may be an effect on the stability of the complex and that this effect would be different from that achieved

in Monahan et al. The loss of cationic polymers may lead to destabilization of the DNA-cationic polymer complex and the effect thereof would be compounded by the effective addition of neutral and anionic polymers to the complex. By contrast, in Monahan et al., the complexes do not loose cationic polymers.

Given the above, Semple et al., Monahan et al., and Trubetskoy et al. do not render applicants' claims obvious and the Examiner's Section 103 rejection of Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 30 based thereon should be withdrawn.

In addition to the above, applicants wish to state for the record that they believe that the arguments made in their July 11, 2005 Reply apply also in that the Examiner has failed to establish a *prima facie* case of obviousness as she has not shown that there exists a suggestion or motivation in the art to combined the cited references to arrive at applicants' invention. As discussed above, Monahan et al. does not suggest the use of CCA or NHS ester to react with cationic lipids/polymers present in a DNA-containing complex but rather the use of CCA in the formation of an anionic polymer which is, in turn, used to form an anionic layer around a DNA-cationic polymer complex. As stated above, one skilled in the art would expect that reacting CCA or NHS ester with the cationic lipids/polymers of a DNA-containing complex would have a completely different effect on the stability of the complex than the simple addition of anionic polymers to form a layer around a DNA-cationic lipid/polymer complex as taught by Monahan et al. Accordingly, one skilled in the art, seeking to use a reagent to modify the DNA-containing complex of Semple et al., would not have been motivated to use CCA (as used in Monahan et al.) and react it with the cationic lipids/polymers therein.

Discussion of the Examiner's Section 112 Rejection

The Examiner rejected Claims 24 to 27, 31, and 32 under Section 112, second

paragraph, because he considered the use of the term "process" therein to be indefinite as it had no antecedent basis. This rejection has been overcome by the above amendments to the claims in which the term "process" has been replaced with --method-- which does have antecedent basis.

Conclusion

In view of the above amendment and remarks, an early and favorable Action is requested respectfully.

Respectfully submitted,

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